Remarks

Applicant respectfully requests reconsideration. Claims 12, 17, 21, 22, 31, 36, 40, 71 and 72 were previously pending in this application. Applicant has amended claims 12, 31, and 71 herewith without prejudice or disclaimer. Support for the amendment can be found throughout the application and the claims as originally filed, for example, on page 4, lines 3-7 and lines 20-23, and in original claims 21, 31, and 40. Applicant has canceled claims 17, 21, 36, 40 and 72 herewith without prejudice or disclaimer and while expressly reserving the right to pursue unclaimed subject matter in one or more continuing applications. As a result, claims 12, 22, 31, and 71 remain pending for examination. No new matter has been added.

Objection to the Oath/Declaration

Applicant acknowledges that the Examiner has withdrawn the objection to the declaration as defective.

Objections to the Specification

Applicant acknowledges that the Examiner has withdrawn the objections to the specification.

Objections to the Claims

Applicant acknowledges that the Examiner has withdrawn the objection to claims 12, 21, 31, 40, 71 and 72 for the recitation of "LKB1". Applicant further acknowledges that the Examiner has withdrawn the objection to claims 12 and 22 for the recitation of the parenthetical phrases "(cells of)" and "(cells)", respectively.

Rejections under 35 U.S.C. § 112, Second Paragraph

Applicant acknowledges that the Examiner has withdrawn the rejection of claims 12, 17, 21-22, 31, 36, 40, and 71-72 as being incomplete for omitting essential elements. Applicant further acknowledges that the Examiner has withdrawn the rejection of claims 21 and 40 as lacking antecedent basis.

The Examiner has maintained the rejection of claims 12, 17, 21, 22, 31, 36, 40, 71 and 72 under 35 U.S.C. § 112, second paragraph, as indefinite. Office Action at page 4. Without

conceding the correctness of the Examiner's position, Applicant has amended the claims and respectfully submits that the rejection under § 112, second paragraph, is moot in view of the claim amendments. Accordingly, Applicant respectfully requests the rejection of the claims as indefinite to be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained the rejection of claims 12, 17, 21, 22, 31, 36 and 40 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Office Action at page 5. Without conceding the correctness of the Examiner's position, Applicant has amended the claims and respectfully submits that the rejection under § 112, first paragraph, is moot in view of the claim amendments. Accordingly, Applicant respectfully requests the rejection of the claims as lacking adequate written description to be withdrawn.

The Examiner has maintained the rejection of claims 12, 17, 21, 22, 31, 36 and 40 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. Office Action at page 8. The Examiner had previously stated that the specification enabled the claims for the compounds recited at page 11, lines 1-10, but did not enable the claims for using any compound that increases or activates AMPK. Page 8 of the Office Action mailed 4/14/2009. Without conceding the correctness of the Examiner's position, Applicant has amended the claims and respectfully submits that the rejection under § 112, first paragraph, is moot in view of the claim amendments. Accordingly, Applicant respectfully requests the rejection of the claims as not enabled to be withdrawn.

Rejections Under 35 U.S.C. § 102

The Examiner has maintained the rejection of claims 31 and 40 under 35 U.S.C. § 102 as anticipated by Shen *et al.* (Clin. Cancer Res. 8:2085-2090, 2002; "*Shen*"). Office Action at page 10. Without conceding the correctness of the Examiner's position, Applicant has amended the claims and respectfully submits that the rejection under § 102 is moot in view of the amendment of claim 31 and the cancellation without prejudice or disclaimer of claim 40. *Shen* does not disclose a method for promoting apoptosis of cells having reduced or absent LKB1 activity,

comprising contacting the cells with phenformin, as recited in the instantly amended claim 31. Therefore, *Shen* does not teach all of the elements of the claimed invention. Accordingly, Applicant respectfully requests the rejection of the claims as anticipated by *Shen* to be withdrawn.

Rejections Under 35 U.S.C. § 102/103

The Examiner has maintained the rejection of claims 12, 17, 21, 31, 36, 40 and 71-72 under 35 U.S.C. § 102, as anticipated by Dilman *et al.* (Arch. Geschwulstforch 48:1-8, 1978; "*Dilman 1*") or Dilman *et al.* (Gerontology 26:241-246, 1980; "*Dilman 2*") as evidenced by *Shen* (as above) and Zhang *et al.* (Am. J. Physiol. Circ. Physiol. 293:H457-H456, 2007; "*Zhang*"). Office Action at page 12. The Examiner's argumentation was summarized on page 13 of the Office Action mailed on April 14, 2009: "Since LKB1 expression is reduced in breast cancer as evidenced by *Shen*, the rats of *Dilman 1* have mammary cancer, phenformin activates AMPK and increases AMPK activity as evidenced by *Zhang*, and phenformin results in a 'slowing or reversing the progression of cancer' in the rats in *Dilman 1*, this anticipates claims 12, 17, 21, 31, 36, 40, and 71-72." The Examiner states that "one of ordinary skill in the art in reading the reference of *Shen* would clearly recognize that breast cancer is a cancer *characterized* by reduced or absent LKB1 activity". Office Action at page 13, emphasis in original.

Without conceding the correctness of the Examiner's position, Applicant has amended the claims to recite a cancer or cells having reduced or absent LKB1 activity. Applicant respectfully submits that the rejection of the claims under §102/103 is moot in view of the claim amendments for at least the reasons set forth below:

First, Applicant respectfully submits that *Shen* fails to evidence that breast cancer is a cancer having reduced or absent LKB1 expression, as recited in the instantly amended claims. As previously submitted, *Shen* teaches that two specific cancer cell lines, MDA-MB-435 and MDA-MB-231, lack LKB1 expression, whereas a third cell line, MCF-7, does not have reduced expression (see Figure 1). In addition, *Shen* shows that LKB1 expression is variable in breast cancer biopsies (see Figure 5 and Table 2). As previously submitted, MDA-MB-435 cells have been shown prior to the earliest priority date of the instant application to <u>not</u> be of breast cancer origin, but rather to have been derived from M14 melanoma cells. See, e.g., Ross *et al.*, Nature Genetics, 24(3):227-235 (March 2000, copy enclosed); and Ellison *et al.*, J Clin Pathol: Mol Pathol 55: 294-299 (October 2002, copy enclosed). Of the two breast cancer cell lines

investigated by *Shen*, only one, MDA-MB-231, exhibited reduced LKB1 activity (See Figure 1). Accordingly, *Shen* teaches that only a subset of breast cancer cell lines exhibits reduced LKB1 expression as reflected in the disclosure of reduced LKB1 expression in breast cancer tissue in only 38 out of 116 breast cancer patients, while 73 patients actually showed increased LKB1 expression (*Shen* at page 2088, left column).

The teachings of *Shen*, accordingly, would not have prompted the skilled artisan to assume that the DMBA-induced mammary tumors of the *Dilman* references would have reduced LKB1 expression.

Second, Applicant submits that the *Dilman* references do not teach 'a method of treating cancer', as recited in claims 12 and 71 or 'a method of promoting apoptosis' as recited in claim 31. Rather, the *Dilman* references teach that phenformin supplementation can reduce DMBA-induced carcinogenesis in rats (*Dilman 1*) and that chronic administration of phenformin can prolong the life of mice and reduce the incidence of sporadic tumors in mice (*Dilman 2*). Accordingly, the *Dilman1* and *Dilman2* references do not teach the treatment of a subject having a cancer, let alone a cancer having reduced or absent LKB1 activity.

The Examiner's statement that "phenformin results in a 'slowing or reversing the progression of cancer' in the rats in *Dilman 1*,"as alleged on page 13 of the Office Action mailed April 14, 2009, is not supported by the reference itself. Nowhere does *Dilman 1* state that progression of established tumors is slowed or reversed. The lower incidence of tumors in phenformin treated rats is instead afforded to the "inhibition of the carcinogenic effect of DMBA by phenformin or by its delay". Page 6, last sentence of the first paragraph of the discussion.

In summary, the cited references, alone or in combination, do not disclose the claimed method of administering phenformin to a subject having a cancer having reduced or absent LKB1 activity, or the claimed method of promoting apoptosis of a cell having reduced or absent LKB1 activity, wherein the reduction of LKB1 activity is due to a mutation or deletion of the LKB1 gene. Accordingly, Applicant respectfully requests the rejection of the claims as anticipated by *Dilman1* or *Dilman2* as evidenced by *Shen* and *Zhang* to be withdrawn.

The Examiner rejected claim 22 under 35 U.S.C. § 102, as anticipated by *Dilman 1* or *Dilman 2* as evidenced by *Shen* and *Zhang* and as further evidenced by Caraci *et al.* (Life Sci.

74:643-650, 2003; "*Caraci*"). The Examiner asserts that *Caraci* teaches that phenformin induces apoptosis of cancer cell lines.

Applicant respectfully submits that the cited references do not anticipate the claims for the same reasons set forth in the traversal above of the rejection made based on *Dilman 1* or *Dilman 2*. *Caraci* does not heal the deficiencies of *Dilman 1* and *Dilman 2*.

Further, as previously submitted, claim 22 recites a method that *further comprises* subjecting the cancer of the subject or cells thereof to a cell death stimulus. This means that the claim recites two steps: (1) administering to a subject having a cancer having reduced or absent LKB1 activity an effective amount of phenformin, as recited in the instantly amended claims,, and (2) subjecting the cancer of the subject or cells thereof to a cell death stimulus. This combination treatment differs from a single treatment, e.g., administration of only phenformin, as is clear from the instant specification, which states: "These results offer the provocative suggestion of a potential therapeutic window in which LKB1-deficient tumor cells might be acutely sensitive to AMP analogues *or sensitized to cell death by other stimuli if treated in combination with AMPK activators*." (Emphasis added, page 37, lines 5-7.).

Accordingly, Applicant respectfully requests reconsideration of the rejection of claim 22 under 35 U.S.C. § 102.

Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 12, 17, 21, 22, 31, 36, 40 and 71-72 under 35 U.S.C. § 103, as unpatentable over the combination of *Dilman1*, *Dilman 2* and Dilman *et al.* (Cancer Lett. 7:357-361, 1979; "*Dilman 3*") as evidenced by *Shen* (as above), *Zhang* (as above) and *Caraci* (as above). Applicant respectfully traverses the rejection.

Applicant respectfully submits that, as outlined previously, the findings that aspects of the claimed invention are based on were unexpected and the skilled artisan could not have had a reasonable expectation of success in making the claimed invention without the knowledge of the particular benefit in increasing AMPK activity in tumors having reduced or absent LKB1 activity, and particularly in tumors where the reduced LKB1 activity is due to a mutation or deletion of the LKB1 gene. The *Dilman* references, alone or in combination, fail to teach that phenformin has an effect on cancers having reduced or absent LKB1 activity and the *Shen* reference fails to heal the deficiencies of the *Dilman* references, because *Shen* teaches that there is variability in

LKB1 expression in breast cancer cell lines and that a majority of breast cancer samples exhibits increased LKB1 expression.

The Examiner asserts that "[a]lthough the teachings of the *Dilman* references do not appear to specifically direct one to administer phenformin to a patient with a cancer having reduced or absent LKB1 activity, based on the teachings of the *Dilman* references that the benefits of phenformin are broad-based and not limited to any particular type of kind of cancer, one would have been motivated to administer phenformin to a patient having *any type or kind of cancer*." Office Action at page 16. The Examiner further asserts that "there is no teaching or suggestion to teach away from administering phenformin to a subpopulation of cancer patients having cancers which reduced or absent LKB1 activity." Id. Further, the Examiner asserts that "the expected beneficial results of administering phenformin are taught by the *Dilman* references and do not require *a priori* knowledge of a nexus between AMPK and LKB1 to practice administering phenformin to a subject having any type or kind of cancer." Id.

In response, Applicant respectfully submits that neither *Dilman 1* nor *Dilman 2* teach administering phenformin to a subject to treat an existing tumor. In both references, the teachings are limited to the inhibition of cancer development through chronic administration of phenformin to healthy subjects. Further, the Examiner's allegation that "the teachings of the *Dilman* references that "the benefits of phenformin are broad-based and not limited to any particular type of kind of cancer" are inconsistent with explicit statements in *Dilman 3*. For example, *Dilman 3* states that "phenformin administered orally to mice at a dose of 2mg/day potentiated the antitumor effect of cyclophosphamide on transplantable squamous cell cervical carcinoma, hepatoma-22a and Lewis lung tumor, but did not alter the effect of cyclophosphamide on sarcoma-180 and L1210." Summary and Table 1 of *Dilman 3*. Accordingly, *Dilman 3* teaches that phenformin potentiates the effect of cyclophosphamide only in specific, but not in all types of tumor cells. Further, *Dilman 3* teaches that administration of phenformin alone did not result in a statistically significant beneficial effect in three out of five cancer cell lines investigated, with respective P-values for phenformin treatment alone being > 0.05. Table 1 and text on page 359. Nowhere does *Dilman 3* teach that the cancers for which an effect of phenformin, either alone or in combination with cyclophosphamide, was observed have reduced LKB1 activity. *Dilman 3* further does not provide any guidance as to how to identify a respondent cell or cancer type.

The Examiner's statement that "while the teachings of the *Dilman* references do not appear to disclose phenformin as increasing AMPK activity in a subject having a cancer with reduced or absent LKB1 activity or to promote apoptosis in cells having reduced or absent LKB1 activity, this is a necessary result of administering phenformin to a subject having such a cancer or to such cells" is insufficient to support an obviousness rejection over these references, because the references fail to teach that any of the cancers disclosed in these references have reduced LKB1 activity, nor do they support an inference of such a reduced activity – the disclosed cancers may very well have had normal or increased LKB1 activity. The *Shen*, *Zhang* and *Caraci* references do not heal these deficiencies. Thus the combination of the cited references does not render obvious the claimed invention.

Accordingly, Applicant respectfully requests reconsideration of the rejection of claims 12, 17, 21, 22, 31, 36, 40 and 71-72 under 35 U.S.C. § 103.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by a payment filed herewith. please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

CANTLEY et al., Applicant

By: /John R. Van Amsterdam/
John R. Van Amsterdam
Reg. No. 40,212
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210
Tel: (617) 646-8000

Docket No. B0662.70057US01
Dated: August 20, 2010
X08/22/10X